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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/888,362	06/22/2001	Patrick J. Muraca	5568/1012	8909

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EXAMINER
SPIEGLER, ALEXANDER H

ART UNIT	PAPER NUMBER
1637	//

DATE MAILED: 07/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/888,362	MURACA, PATRICK J.	
	Examin r	Art Unit	
	Alexander H. Spiegler	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *April 14th, 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-69* is/are pending in the application.

4a) Of the above claim(s) *16-34 and 66-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 35-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5, 10 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to Paper No. 9, filed on April 14th, 2003. Currently, claims 1-69 are pending.

2. Applicant's confirmation of the election of Group I, claims 1-15 and 35-65 in Paper No. 9 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 1-15 and 35-65 are rejected; and claims 16-34 and 66-69 have withdrawn from consideration, as being drawn to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

4. This action is made FINAL.

MAINTAINED REJECTIONS

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-15 and 35-65 rejected under 35 U.S.C. 103(a) as being unpatentable over Leighton (USPN 6,103,518), in view of Irving et al. (J of Clin. Path. (1996) 49: 258-259).

Leighton teaches a method for constructing tissue microarrays (also referred to as "tissue Chips") comprising,

"taking samples from a series of donor tissues, one at a time, using a hollow, preferably needlelike, donor punch and placing each sample sequentially in a recipient of complementary shape in a recipient material by a recipient punch, thereby forming an array of tissues in the recipient block. Each punch comprises a punch tube and an associated stylet guided within the diameter approximating that of the donor punch inner diameter, and is dimensioned for sliding within the punch tube. The process of forming a hole in a recipient material such as paraffin, taking a sample of tissue from a donor specimen, and planting this sample in the hole in the recipient material, is repeated until a tissue array is formed comprising hundreds of tissue samples arranged in assigned locations in the recipient material. (col. 7).

"Once the desired number of tissue samples have been transplanted from the donor block(s) to the recipient block, the "tissue chips" can be formed by slicing the tissue array block into hundreds of consecutive thin sections of, e.g., 5 micrometers in thickness, by traditional means (i.e., microtomes such as Model Cut .sub. 4055.TM. by Olympus Corp. of Tokyo, Japan, etc.; see, e.g., U.S. Pat. Nos. 664,118; 2,292,973; 2,680,992; 3,420,130; 3,440,913; 3,496,819; 3,799,029; and 3,975,977) to create multiple nearly identical sections, with each of the donor cores then being represented as minuscule dots on an ordinary glass microscope slide. Analyses that may be performed on the donor specimens include immunological analysis, nucleic acid hybridization, and clinicopathological characterization of the specimen." (col. 13).

Leighton also teaches:

"The sample punched from the donor tissue sample is preferably cylindrical, about 1-8 mm in length, with a diameter of from about 0.4 to 4.0 mm, preferably about 0.3-2.0 mm. The recipient punch is slightly smaller than the donor punch and is used to create a hole in a recipient block, typically made of paraffin or other embedding medium." (col. 7).

Leighton also teaches that the methods can be automated and information for each donor sample in the recipient block is stored in a database (col. 7). Leighton also teaches that this array can be used for many types of samples, including diseased samples (col. 1-4). It is also noted, that with respect to claims 54-65 (claims drawn to contacting the microarray with a molecular probe), Leighton teaches that the array made in his methods can be used in nucleic acid hybridization, which would inherent use a molecular probe for detection (e.g., determining which sublocation react).

Leighton teaches that the tissue samples are embedded in a block of paraffin or other embedding material. Leighton does not specifically teach the use of frozen embedding material.

However, Irving teaches that storing pathological tissue or cell specimens in OCT embedding material (i.e., a frozen embedding material) "permits retrospective analysis of RNA from small amounts of stored pathological samples" (see abstract). In other words, Irving teaches that embedding samples in OCT embedding material produces high quality RNA (i.e., RNA is not likely to get degraded in OCT, as it would in paraffin embedding material) (pg. 258).

In view of the teachings of Irving, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Leighton so as to have embedded tissue and/or cell samples in OCT embedding material, in order to have achieved the benefit of providing a higher quality RNA, which would help obtain better results when analyzing the tissue and/or cell samples in subsequent molecular analysis (such as expression analysis).

7. Claims 1-15 and 35-65 rejected under 35 U.S.C. 103(a) as being unpatentable over Leighton (USPN 6,103,518), in view of Goldsworthy et al. (Mol. Carcinog (1999) 25(2): 86-91).

The teachings of Leighton are presented above. Specifically, Leighton teaches the preparation of a tissue microarray, wherein the tissue samples are embedded in a block of paraffin or other embedding material. Leighton does not specifically teach the use of frozen embedding material.

However, Goldsworthy teaches that "frozen tissues yielded more RT-PCR product than did paraffin-embedded tissues" when analyzing liver tissue expression (see abstract and pg. 87). Goldsworthy concludes that one of the reasons for this that, "the longer exposure of the fresh tissues to the fixative before embedding in paraffin may have resulted in RNA degradation from endogenous RNases, resulting in lower amounts of amplifiable RNA" (pg. 90, second column).

Goldsworthy results, like others in the art, further support the idea that better results of amplification of RNA from tissues are obtained by using methods other than paraffin blocks (pg. 90, second column).

In view of the teachings of Goldsworthy, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Leighton so as to have embedded tissue and/or cell samples in a frozen embedding material, in order to have achieved the benefit of providing a higher quality RNA, which would help obtain better results when analyzing the tissue and/or cell samples in subsequent molecular analysis (such as expression analysis).

Response to Applicant's Arguments for the Combination of Leighton and Irving (or Goldsworthy)

MPEP 2143 states:

> To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The combination of Leighton and Irving (or Goldsworthy) teach all of the claim limitations.

Leighton teaches a method of preparing a tissue microarray and a tissue microarray using paraffin or other embedding material (see teachings above and for example, col. 7, ln. 22-24). Irving teaches the advantages of embedding tissue and/or cell samples in OCT embedding (i.e., a frozen embedding material). Goldsworthy teaches "the longer exposure of the fresh tissues to the fixative before embedding in paraffin may have resulted in RNA degradation from

endogenous RNases, resulting in lower amounts of amplifiable RNA" (pg. 90, second column). Goldsworthy concludes that higher quality RNA is obtained when tissues are frozen, as opposed to embedding tissues in paraffin (pgs. 86 and 90, second column, for example).

Accordingly, the combination of Leighton and Irving (or Goldsworthy) teach all of the claim limitations.

Irving's (or Goldsworthy's) teachings would have motivated one of ordinary skill to have used a frozen embedding material in order produce high quality RNA for further analysis.

Irving teaches that storing pathological tissue or cell specimens in OCT embedding material (i.e., a frozen embedding material) "permits retrospective analysis of RNA from small amounts of stored pathological samples" (see abstract). In other words, Irving teaches that embedding samples in OCT embedding material produces high quality RNA (i.e., RNA is not likely to get degraded in OCT, as it would in paraffin embedding material) (pg. 258). Accordingly, Irving's teachings would have motivated one of ordinary skill in the art to have used frozen embedding material, such as OCT, instead of paraffin embedding material, in order to avoid the degradation of RNA, and therefore, have better quality analysis following the embedding and storing process. Likewise, Goldsworthy teaches the disadvantages of embedding tissues in paraffin, and finds that embedding tissues in a frozen material leads to higher quality RNA for use in further analysis (see pgs. 86 and 88-90). Accordingly, Goldsworthy teachings would have motivated one of ordinary skill in the art to have used frozen embedding material, instead of paraffin embedding material, in order to avoid the degradation of RNA, and therefore, have better quality analysis following the embedding and storing process.

The skilled artisan would have had a reasonable expectation of success for using a frozen embedding medium in the methods of Leighton.

First, the teachings of Leighton suggest that other embedding media are acceptable in carrying out his method (see teachings above and col. 7, ln. 22-24). Furthermore, the non-Hodgkin's lymphoma tissue samples embedded in Irving's OCT embedding material (or the liver tissue samples used by Goldsworthy) are the same types of samples (e.g., tissue samples) in which Leighton seeks to embed. Finally, absent any evidence to the contrary, there is no reason to believe there is not a reasonable expectation of success.

Accordingly, the combination of Leighton and Irving (or Goldsworthy) satisfies the three basic criteria necessary to establish a prima facie case of obviousness.

Applicants argue neither Irving nor Goldswothy discloses, "using the frozen tissue to construct a frozen tissue microarray" (pg. 3 of Applicant's response, see also pg. 8). This argument is not convincing because the test of obviousness under 35 U.S.C. 103 is not express suggestion of the claimed invention in any or all of the references but what references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them (*In re Rosselet*, 146 USPQ 183(CCPA 1965). The fact that Irving (or Goldsworthy) does not itself teach a combination of all of the claim limitations only mitigates against using this reference as an anticipatory reference, not as evidence in reaching a conclusion of obviousness under 35 U.S.C. 103. As reiterated above, the combination of Leighton and Irving (or Goldsworthy) teach all of the limitations of the claims.

Applicant's also argue Leighton does not teach that his method could be adapted to use a frozen embedding matrix. However, as stated above, Leighton suggests using material other

than paraffin, and Irving (and Goldsworthy) teach the advantages for using a frozen embedding matrix and sample.

Accordingly, the rejection is MAINTAINED.

8. Claims 1-15 and 35-65 rejected under 35 U.S.C. 103(a) as being unpatentable over Kallioniemi et al. (Pub. No. US 2002/0132246), in view of Irving et al. (J of Clin. Path. (1996) 49: 258-259).

Kallioniemi teaches a method for making a tissue microarray:

"In a specific example, core tissue biopsies having a diameter of 0.6 mm and a height of 3-4 mm, were taken from selected representative regions of individual "donor" paraffin-embedded tumor blocks and precisely arrayed into a new "recipient" paraffin block (20 mm.times.45 mm). H&E-stained sections were positioned above the donor blocks and used to guide sampling from morphologically representative sites in the tumors. Although the diameter of the biopsy punch can be varied, 0.6 mm cylinders have been found to be suitable because they are large enough to evaluate histological patterns in each element of the tumor array, yet are sufficiently small to cause only minimal damage to the original donor tissue blocks, and to isolate reasonably homogenous tissue blocks.

With the adhesive film in place, a 4-8 .mu.m section of the recipient block is cut transverse to the longitudinal axis of the tissue cylinders (FIG. 5) to produce a thin microarray section 76 (containing tissue specimen cylinder sections in the form of disks) that is transferred to a conventional specimen slide 78. The microarray section 76 is adhered to slide 78, for example by adhesive on the slide. The film 74 is then peeled away from the underlying microarray member 76 to expose it for processing. A darkened edge 80 of slide 78 is suitable for labeling or handling the slide." (pg. 5, Figs. 1-10 and 15-17).

Kallioniemi teaches that the samples can be that the methods can be automated and information for each donor sample in the recipient block is stored in a database (pg. 5, for example). Additionally, Kallioniemi teaches microarray can be used for many types of samples, including diseased samples (pgs. 1-4, Ex. 1-14). Kallioniemi also teaches methods including contacting the microarray with a molecular probe (pgs. 1-4, for example).

Kallioniemi does not specifically teach the use of frozen embedding material.

However, Irving teaches that storing pathological tissue or cell specimens in OCT embedding material (i.e., a frozen embedding material) "permits retrospective analysis of RNA from small amounts of stored pathological samples" (see abstract). In other words, Irving teaches that embedding samples in OCT embedding material produces high quality RNA (i.e., RNA is not likely to get degraded in OCT, as it would in paraffin embedding material) (pg. 258).

In view of the teachings of Irving, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kallioniemi so as to have embedded tissue and/or cell samples in OCT embedding material, in order to have achieved the benefit of providing a higher quality RNA, which would help obtain better results when analyzing the tissue and/or cell samples in subsequent molecular analysis (such as expression analysis).

9. Claims 1-15 and 35-65 rejected under 35 U.S.C. 103(a) as being unpatentable over Kallioniemi et al. (Pub. No. US 2002/0132246), in view of Goldsworthy et al. (Mol. Carcinog (1999) 25(2): 86-91).

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Goldsworthy results, like others in the art, further support the idea that better results of amplification of RNA from tissues are obtained by using methods other than paraffin blocks (pg. 90, second column).

In view of the teachings of Goldsworthy, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kallioniemi so as to have embedded tissue and/or cell samples in a frozen embedding material, in order to have achieved the benefit of providing a higher quality RNA, which would help obtain better results when analyzing the tissue and/or cell samples in subsequent molecular analysis (such as expression analysis).

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The combination of Kallioniemi and Irving (or Goldsworthy) teach all of the claim limitations.

Kallioniemi teaches a method of preparing a tissue microarray and a tissue microarray using paraffin or other embedding material (see for example, col. 18, paragraph 0195). Irving teaches the advantages of embedding tissue and/or cell samples in OCT embedding (i.e., a frozen embedding material). Goldsworthy teaches "the longer exposure of the fresh tissues to the fixative before embedding in paraffin may have resulted in RNA degradation from endogenous RNases, resulting in lower amounts of amplifiable RNA" (pg. 90, second column). Goldsworthy

concludes that higher quality RNA is obtained when tissues are frozen, as opposed to embedding tissues in paraffin (pgs. 86 and 90, second column, for example).

Accordingly, the combination of Kallioniemi and Irving (or Goldsworthy) teach all of the claim limitations.

Irving's (or Goldsworthy's) teachings would have motivated one of ordinary skill to have used a frozen embedding material in order produce high quality RNA for further analysis.

Irving teaches that storing pathological tissue or cell specimens in OCT embedding material (i.e., a frozen embedding material) "permits retrospective analysis of RNA from small amounts of stored pathological samples" (see abstract). In other words, Irving teaches that embedding samples in OCT embedding material produces high quality RNA (i.e., RNA is not likely to get degraded in OCT, as it would in paraffin embedding material) (pg. 258). Accordingly, Irving's teachings would have motivated one of ordinary skill in the art to have used frozen embedding material, such as OCT, instead of paraffin embedding material, in order to avoid the degradation of RNA, and therefore, have better quality analysis following the embedding and storing process. Likewise, Goldsworthy teaches the disadvantages of embedding tissues in paraffin, and finds that embedding tissues in a frozen material leads to higher quality RNA for use in further analysis (see pgs. 86 and 88-90). Accordingly, Goldsworthy teachings would have motivated one of ordinary skill in the art to have used frozen embedding material, instead of paraffin embedding material, in order to avoid the degradation of RNA, and therefore, have better quality analysis following the embedding and storing process.

The skilled artisan would have had a reasonable expectation of success for using a frozen embedding medium in the methods of Kallioniemi.

First, the teachings of Kallioniemi suggest that other embedding media are acceptable when carrying out his method, especially when multiple biopsy specimens are obtained from surgery (which are regularly embedded in frozen media) (see for example, col. 18, paragraph 0195). Furthermore, the non-Hodgkin's lymphoma tissue samples embedded in Irving's OCT embedding material (or the liver tissue samples used by Goldsworthy) are the same types of samples (e.g., tissue samples) in which Kallioniemi seeks to embed. Finally, absent any evidence to the contrary, there is no reason to believe there is not a reasonable expectation of success.

Accordingly, the combination of Kallioniemi and Irving (or Goldsworthy) satisfies the three basic criteria necessary to establish a prima facie case of obviousness.

Applicants argue neither Irving nor Goldswothy discloses, "using the frozen tissue to construct a frozen tissue microarray" (pg. 3 of Applicant's response, see also pg. 8). This argument is not convincing because the test of obviousness under 35 U.S.C. 103 is not express suggestion of the claimed invention in any or all of the references but what references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them (*In re Rosselet*, 146 USPQ 183(CCPA 1965). The fact that Irving (or Goldsworthy) does not itself teach a combination of all of the claim limitations only mitigates against using this reference as an anticipatory reference, not as evidence in reaching a conclusion of obviousness under 35 U.S.C. 103. As reiterated above, the combination of Leighton and Irving (or Goldsworthy) teach all of the limitations of the claims.

Applicant's also argue Kallioniemi does not teach that his method could be adapted to use a frozen embedding matrix. However, as stated above, Kallioniemi suggests using material

other than paraffin, and Irving (and Goldsworthy) teach the advantages for using a frozen embedding matrix and sample.

Conclusion

10. No claims are allowable.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (703) 305-0806. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014. Applicant is also invited to contact the TC 1600 Customer Service Hotline at (703) 308-0198.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Alexander H. Spiegler
July 10, 2003

CARLA J. MYERS
PRIMARY EXAMINER